Original article

Do post-COVID-19 symptoms exist? A longitudinal study of COVID-19 sequelae in Wenzhou, China

Les symptômes post-COVID-19 existent-ils ? Une étude longitudinale des séquelles du COVID-19 à Wenzhou, Chine

Min Zhou [a,1], Jing Cai [b,1], Wenjie Sun [c,d,1], Jing Wu [e], Yidong Wang [f], Michelle Gamber [g], Lingyan Fan [h,*], Guiqing He [i,**]

[a] *Department of infectious diseases, Xinyu people's hospital, 338000 Xinyu city, Jiangxi province, China*
[b] *Department of comprehensive medicine, Wenzhou Central Hospital Medical Group, Affiliated Dingli Clinical Institute of Wenzhou Medical University, 325000 Wenzhou, Zhejiang province, China*
[c] *The Second affiliated hospital of Fujian traditional Chinese medical university, 350003 Fuzhou city, Fujian province, China*
[d] *Robert Stempel college of public health and social work, Florida international university, 33199 Miami, Florida, United States of America*
[e] *Department of infectious diseases, Huashan hospital, Fudan university, 200040 Shanghai, China*
[f] *Department of geriatrics, Wenzhou central hospital, 325000 Wenzhou, Zhejiang province, China*
[g] *School of health professions, Division of public health, Shenandoah University, 22601 Winchester, United States of America*
[h] *Department of acute infection, Hwa Mei hospital, University of Chinese academy of sciences, No. 175, Yongfeng north road, Jiangbei district, 315000 Ningbo city, Zhejiang province, China*
[i] *Department of infectious diseases and infectious diseases laboratory, Wenzhou sixth people's hospital, Wenzhou central hospital medical group, Affiliated Dingli clinical institute of Wenzhou medical university, No. 252, Baili East road, 325000 Wenzhou, Zhejiang province, China*

A R T I C L E   I N F O

A B S T R A C T

Objective. – We conducted a cohort of tracing discharge patients of COVID-19.
Materials and methods. – We used the Mann–Whitney U test, χ^2 test, or Fisher's exact test to compare differences between age groups and gender groups where appropriate.
Results. – Our study provides insights into the nature and severity of medical conditions specific to survivors of COVID-19.
Conclusions. – It also highlights the potential mental health issues resulting from infectious disease outbreaks within communities.
© 2021 The Authors. Published by Elsevier Masson SAS. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

R É S U M É

Objectifs. – Nous avons suivi une cohorte de patients à la sortie du COVID-19.
Matériaux et méthodes. – Nous avons utilisé les test de Mann–Whitney U, de Fisher ou du Chi[2] pour comparer les différences entre les groupes d'âge et de genre, le cas échéant.
Résultats. – Notre étude fournit un aperçu de la nature et de la gravité des troubles médicaux propres aux survivants du COVID-19.
Conclusions. – Elle met également en lumière les problèmes de santé mentale potentiels découlant des éclosions de maladies infectieuses dans les collectivités.
© 2021 Les Auteurs. Publié par Elsevier Masson SAS. Cet article est publié en Open Access sous licence CC BY-NC-ND (http://creativecommons.org/licenses/by-nc-nd/4.0/).

---

* Corresponding author.
** Co-corresponding author.
E-mail addresses: fanlinyan12345@163.com (L. Fan), hegq123@126.com (G. He).
[1] These authors contributed equally to the work.

1. Abbreviations

COVID-19 The novel Coronavirus
PTSD   Post-traumatic stress disorder
PCL-C   PTSD checklist–civilian version
CT   computed tomography

2. Introduction

The novel Coronavirus (COVID-19) outbreak occurred in Wuhan, China in December 2019 and spread to other countries. Most patients' symptoms have been mild to moderate and have been resolved after receiving therapy.

The outbreak of COVID-19 in China has been defined by the World Health Organisation as a public health emergency of international concern. The epidemic not only causes social panic, but also causes physical and mental damage to people.

However, little is known about the patient's health status or disease prognosis when the COVID-19 patients are discharged from hospitals. Moreover, recurrence of positive SARS-CoV-2 RNA has been reported [1]. Of note, post-traumatic stress disorder (PTSD) had been reported in other fatal virus infectious diseases [2,5,6]. Most previous studies have focused on the effects of public health emergencies on post-traumatic stress disorder in medical staff (PTSD), but there are few studies on traumatic stress disorder in patients. To the best of our knowledge, there are no studies reporting on the status of discharged COVID-patients. Hence, we conducted a prospective study on the COVID-19 patients from Wenzhou.

3. Methods

3.1. Patients

Until February 14, there were 139 confirmed COVID-19 cases admitted in Wenzhou sixth people's hospital. Among them, 89 discharged patients were followed up during at least 3 weeks with a semi-structured questionnaire address on post-COVID-19 symptoms and health status. The surveys collected information on symptoms and diagnostic testing occurring any time during the recovery period. Mental health status was also assessed by administering the PTSD checklist–civilian version (PCL-C) [9]. The ethics commissions of Wenzhou central hospital medical group hospital approved the study.

The participants responded to the PLC-C, which includes 17 items on a 5-point scale, ranging from 1 (not at all) to 5 (extremely) in three areas: Intrusion, avoidance and numbing, and hyperarousal. A PTSD severity score was computed by summing up all symptom scores. Respondents indicated the extent to which they have been affected by symptoms over the past month. The PCL-C total score ranges from 17 to 85, with higher scores indicating greater PTSD symptom severity. It was recommended that, when the instrument was used as a continuous measure, a cut-off score of 50 is optimal for making the diagnosis of combat related PTSD. The scores that range from 38–49 suggest probable PTSD.

The protocol was approved by the review board at the Wenzhou central hospital. Written informed consent was obtained from all participants.

3.2. Discharge criteria

According to the national criteria, the discharge criteria were:

- afebrility for at least 3 days;
- obvious alleviation of respiratory symptoms;
- improvement in radiological abnormalities on chest computed tomography (CT) or X-ray;
- and two consecutive negative detections of SARS-CoV-2 at least 24 h apart [10].

3.3. Statistical analysis

Continuous and categorical variables were presented as median (IQR) and n (%), respectively. We used the Mann–Whitney U test, χ^2 test, or Fisher's exact test to compare differences between age groups and gender groups where appropriate. The prevalence of the total prevalence of symptom or sign was estimated with 95% confidence intervals. All tests were 2-sided, and a P value less than 0.05 was considered statistically significant. All statistical analyses were performed by the SPSS software, version 19.0 (IBM Corp, Armonk, NY).

4. Results

Of 89 patients (median 43 years [IQR 31–52]), 43 were female (Table 1). Of note, six patients (6.7%) had a recurrence of positive RNA at the three-week follow-up. Several symptoms were reported by the discharged patients, e.g. mild (e.g., fatigue) to more severe complications requiring rehospitalisation or treatment. The most frequently reported symptoms were cough (46.1%), fatigue (36.0%), expectoration properties (24.7%) (coughing up or spitting up material from the respiratory track), chest tightness and insomnia (Table 1). Six patients (6.7%) had fever (oral temperature higher than 37.4°C). Three patients (3.4%) complained of poor appetite, while two patients (2.2%) complained of myalgia, arthralgia, oral ulcers and eye discomfort respectively.

Altogether, thirty-eight of the patients (42.7%) felt completely improved, and forty-two patients (47.2%) felt much improved, with one patient feeling no improvement and another patient feeling even worse. There was no significant difference in symptoms, signs or RT-PCR conversion between the age and sex groups ($P > 0.05$).

Only 73 patients were assessed for psychological stress by administering the PTSD checklist–civilian version (PCL-C) (Table 2). There were sixteen patients, more likely to be females aged over 45 years, who did not participate in the mental health assessment. Eleven percent of the survivors had probable post-traumatic stress disorder (PTSD) and 13.7% of the survivors, who manifested high distress and with trauma exposure, had PTSD. Females had higher scores of PTSD than males ($P = 0.001$), but there was no significant difference between age groups.

5. Discussion

Post-COVID-19 symptoms include, but are not restricted to, musculoskeletal pain, headache, and ocular problems. Our results are consistent with previous studies of similar infectious diseases, such as Ebola, SARS, and MERS that result in emergency conditions [4,7,8]. Most symptoms reported in the present study are not specific, which could be due to previous chronic disease conditions patients already suffer from, or it could be temporary symptoms related to COVID-19. It might resolve in the future. However, long-term follow-up is needed.

Recurrence of positive SARS-CoV-2 RNA is a unique phenomenon. It is different from coronaviruses, such as SARS and MERS, which do not similarly reported relapses in the literature resulting among discharged patients. In the present study, there were 6 cases among 89 discharge patients (6.7% with 95% CI [1.4–12.1]). The mechanism is still unclear until now. The potential explanation is

Table 1

Selected signs and symptoms reported by COVID-19 patients 3 weeks after discharge.

Symptoms or signs	Total (n=89) No. (% [95% CI])	Age, No. (%)			Gender, No. (%)		
		< 45y (n=47)	≥ 45y (n=42)	P value	Female (n=43)	Male (n=46)	P value
Fever	6 (6.7 [1.4–12.1])	3 (6.4)	3 (7.1)	1.000	4 (9.3)	2 (4.3)	0.424
Cough	41 (46.1 [35.5–56.6])	20 (42.6)	21 (50)	0.528	20 (46.5)	21 (45.7)	1.000
Expectoration	22 (24.7 [15.6–33.9])	9 (19.1)	13 (31.0)	0.418	11 (25.6)	11 (23.9)	0.706
Fatigue	32 (36.0 [25.8–46.1])	14 (29.8)	18 (42.9)	0.269	18 (41.9)	14 (30.4)	0.279
Diarrhea	16 (18.0 [9.8–26.1])	9 (19.1)	7 (16.7)	0.790	7 (16.3)	9 (19.6)	0.786
Chest tightness	22 (24.7 [15.6–33.9])	10 (21.3)	12 (28.6)	0.468	13 (30.2)	9 (19.6)	0.634
Poor appetite	3 (3.4 [0–7.2])	0 (0.0)	3 (7.1)	0.101	4 (9.3)	0 (0.0)	0.051
Insomnia	22 (24.7 [15.6–33.9])	9 (19.1)	13 (31.0)	0.226	13 (30.2)	9 (19.6)	0.326
Recurrence of positive SARS-CoV-2 RNA	6 (6.7 [1.4–12.1])	4 (8.5)	2 (4.8)	0.680	3 (7.0)	3 (6.5)	1.000
General recovery				1.000			1.000
Complete improvement	38 (42.7 [32.2–53.2])	25 (53.2)	13 (31.0)		19 (44.2)	19 (41.3)	
Much improvement	42 (47.2 [36.6–57.8])	21 (44.7)	21 (50)		16 (37.2)	26 (56.5)	
Slight improvement	7 (7.9 [2.2–13.6])	1 (2.1)	6 (14.3)		6 (14.0)	1 (2.2)	
No improvement	1 (1.1 [0–3.4])	0 (0.0)	1 (2.4)		1 (2.3)	0 (0.0)	
Worse	1 (1.1 [0–3.4])	0 (0.0)	1 (2.4)		1 (2.3)	0 (0.0)	

Table 2

PTSD checklist–civilian version (PCL-C) by COVID-19 patients after discharge.

	Total (n=73) No. (% [95% CI])	Age, No. (%)			Gender, No. (%)		
		< 45y (n=42)	≥ 45y (n=31)	P value	Female (n=33)	Male (n=40)	P value
Median (IQR)	28.0 (20.0–40.0)	27.5 (18.8–44.3)	28.0 (22.0–37.0)	0.942	31.0 (27.5–43.0)	23.0 (17.0–34.0)	0.001
Normal score = 0~37	55 (75.3 [65.2–85.5])	30 (71.4)	25 (80.6)	1.000	22 (66.7)	33 (82.5)	1.000
Probable PTSD score = 38~49	8 (11.0 [3.6–18.3])	4 (9.5)	4 (12.9)		5 (15.2)	3 (7.5)	
PTSD score ≥ 50	10 (13.7 [5.6–21.8])	8 (19.0)	2 (6.4)		6 (18.2)	4 (10.0)	

that health systems are being overwhelmed and are not able to adequately follow up with patient's post-discharge. The hospitals are often forced to discharge these patients, even if they haven't fully recovered, as the need for beds is immense. Future studies on the clinical symptoms of those patients and pathology are warrant.

COVID-19 pandemic has been associated with increases in mental health issues among COVID-19 patients. Typically, PTSD is triggered by a terrifying or traumatic event, which could result from either experiencing it or witnessing it. As for COVID-19, the emergency environmental conditions that have been induced with this infectious disease might produce unique characteristics that are resulting in PTSD among COVID-19 survivors. Of note, most COVID-19 patients are more likely to be infected by close contact from family members, for example. As a result, those patients might be experiencing the impacts of both COVID-19 exposure in themselves as well as witnessing it in their family member. This could result in a double exposure effect and could have a more severe impact. Also, our results confirm that gender difference exists in PTSD [3]. It could be due to the hormone and neurosteroid/peptide differences from both pre-clinical and clinical research [3].

6. Limitations

Our study has several limitations. Dysfunctional information related to complained symptoms was not accessed. Most symptoms were self-reported and were not crosschecked against medical charts. Also, follow-up time since hospital discharge was short, and PTSD symptoms can manifest years after the traumatic situation has occurred. The pathogenesis of the symptoms reported by survivors of COVID-19 is unclear and requires further study.

7. Implications

Our study provides insights into the nature and severity of medical conditions specific to survivors of COVID-19. It also highlights the potential mental health issues resulting from infectious disease outbreaks within communities. The long-term consequences may not just be physical symptoms, which could necessitate comprehensive and coordinated mental health responses. Lastly, this study has underscored the importance of better understanding the conditions that lead to reinfection and what this means for measures that are undertaken to decrease disease transmission.

8. Conclusion

Long-term psychological support could be a crucial element aiding in reducing mortality and morbidity, and promoting overall effectiveness of efforts to halt COVID-19 transmission. This study provides a reference for improving people's mental health and psychological adaptability during any future COVID-19-like pandemic.

Disclosure of interest

The authors declare that they have no competing interest.

Ethics approval

The ethics commissions of Wenzhou central hospital medical group hospital approved the study.

Statement of informed consent

Written informed consent was obtained from a legally authorised representative(s) for anonymised patient information to be published in this article.

Availability of data and materials

All data generated or analysed during this study are included in this published article.

Authors' contributions

Min Zhou, Jing Cai and Wenjie Sun designed the study, and supervised the data collection; Jing Wu, Yidong Wang and Michelle Gamber analysed and interpreted the data; Lingyan Fan and Guiqing He prepared the manuscript for publication and reviewed the draft of the manuscript. All authors have read and approved the manuscript.

References

[1] Chen D, Xu W, Lei Z, Huang Z, Liu J, Gao Z, et al. Recurrence of positive SARS-CoV-2 RNA in COVID-19: a case report. Int J Infect Dis 2020;93:297–9.

[2] Group PIS.. A longitudinal study of Ebola sequelae in Liberia. N Engl J Med 2019;380(10):924–34.

[3] Kornfield SL, Hantsoo L, Epperson CN. What does sex have to do with it? The role of sex as a biological variable in the development of post-traumatic stress disorder. Curr Psychiatry Rep 2018;20(6):39.

[4] Lee SH, Shin H-S, Park HY, Kim JL, Lee JJ, Lee H, et al. Depression as a mediator of chronic fatigue and post-traumatic stress symptoms in Middle East respiratory syndrome survivors. Psychiatry Invest 2019;16(1):59.

[5] Lee SM, Kang WS, Cho A-R, Kim T, Park JK. Psychological impact of the 2015 MERS outbreak on hospital workers and quarantined hemodialysis patients. Compr Psychiatry 2018;87:123–7.

[6] Mak IWC, Chu CM, Pan PC, Yiu MGC, Chan VL. Long-term psychiatric morbidities among SARS survivors. Gen Hosp Psychiatry 2009;31(4):318–26.

[7] Scott JT, Sesay FR, Massaquoi TA, Idriss BR, Sahr F, Semple MG. Post-Ebola syndrome, Sierra Leone. Emerg Infect Dis 2016;22(4):641.

[8] Siu JYm. Coping with future epidemics: tai chi practice as an overcoming strategy used by survivors of severe acute respiratory syndrome (SARS) in post-SARS Hong Kong. Health Expect 2016;19(3):762–72.

[9] Wilkins KC, Lang AJ, Norman SB. Synthesis of the psychometric properties of the PTSD checklist (PCL) military, civilian, and specific versions. Depress Anxiety 2011;28(7):596–606.

[10] Zhao J-Y, Yan J-Y, Qu J-M. Interpretations of "Diagnosis and treatment protocol for novel Coronavirus pneumonia (trial version 7)". Chin Med J 2020;133(11):1347–9.